CME Review article

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Intolerance to dietary biogenic amines: a review

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Objective: To evaluate the scientific evidence for purported intolerance to dietary biogenic amines.

Data Sources: MEDLINE was searched for articles in the English language published between January 1966 and August 2001. The keyword *biogenic amin** was combined with *hypersens*, allerg*, intoler**, and *adverse*. Additionally, the keywords *histamine*, *tyramine,* and *phenylethylamine* were combined with *headache*, *migraine*, *urticaria*, *oral challenge,* and *oral provocation*. Articles were also selected from references in relevant literature.

Study Selection: Only oral challenge studies in susceptible patients were considered. Studies with positive results (ie, studies in which an effect was reported) were only eligible when a randomized, double-blind, placebo-controlled design was used. Eligible positive result studies were further evaluated according to a number of scientific criteria. Studies with negative results (ie, studies in which no effect was reported) were examined for factors in their design or methods that could be responsible for a false-negative outcome. Results of methodologically weak or flawed studies were considered inconclusive.

Results: A total of 13 oral challenge studies (5 with positive results and 8 with negative results) were found. Three of them (all with positive results) were considered ineligible. By further evaluation of the 10 eligible studies, 6 were considered inconclusive. The 4 conclusive studies all reported negative results. One conclusive study showed no relation between biogenic amines in red wine and wine intolerance. Two conclusive studies found no effect of tyramine on migraine. One conclusive study demonstrated no relation between the amount of phenylethylamine in chocolate and headache attacks in individuals with headache.

Conclusions: The current scientific literature shows no relation between the oral ingestion of biogenic amines and food intolerance reactions. There is therefore no scientific basis for dietary recommendations concerning biogenic amines in such patients.

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INTRODUCTION

Biogenic amines are organic bases with low molecular weight. They are synthesized by decarboxylation of free amino acids in microbial, vegetable, and animal metabolisms. As a result, they occur naturally in many foods but can also be produced in foods by bacteria as part of the production process (fermentation) or during storage or decay. Foods containing considerable amounts of biogenic amines are yeast extracts, fish, chocolate, alcoholic drinks, and fermented products, such as cheese, soy products, sauerkraut, and processed meat.[1]

The possibility that dietary biogenic amines might cause adverse reactions was initially proposed when it was noticed that foods that caused symptoms in patients taking monoamine oxidase–inhibiting drugs were the same as those believed to cause migraine attacks in some patients.[2] The foods implicated were cheese, alcoholic beverages (mainly red wine), fish, and chocolate. When a number of cheeses were analyzed, it was found that they contained large amounts of tyramine, a biogenic monoamine with strong vasoconstrictive properties.[3] Although tyramine is not a main constituent of all the other foods named, a relation between the ingestion of tyramine and headache was proposed.

A number of adverse reactions have been subsequently ascribed to dietary biogenic amines. The relation between tyramine and migraine has been studied most extensively, although headache purportedly resulting from phenylethylamine ingestion (another vasoconstrictive monoamine) has also received considerable attention. Urticaria has often been linked to tyramine but also to histamine, a vasodilatory diamine. Furthermore, a number of symptoms have been alleged to be caused by dietary histamine, namely, headaches, decrease in blood pressure, flushing, sneezing, and respiratory and gastrointestinal distress. Our literature search located no reports to date of adverse reactions to other biogenic amines (eg, tryptamine, serotonin, putrescine, and spermine).

Since 1984 the databank ALBA (ALlergen dataBAnk, TNO Nutrition and Food Research, Zeist, the Netherlands) has gathered information about the presence of substances in food that might cause hypersensitivity reactions. The aim of ALBA is to give such patients the opportunity to choose

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foods less likely to cause adverse reactions. As a part of quality assurance for ALBA, we evaluated the scientific evidence for purported intolerance to dietary biogenic amines.

METHODS

To evaluate the relation between dietary biogenic amines and food intolerance, a literature search was conducted in MEDLINE for articles published between January 1966 and August 2001. The search was limited to articles in the English language and to words in the title and/or abstract. The keyword *biogenic amin** was combined with *hypersens*, allerg*, intoler*,* and *adverse*. Additionally, the keywords *histamine*, *tyramine,* and *phenylethylamine* were combined with *headache*, *migraine*, *urticaria*, *oral challenge,* and *oral provocation*. Searches with *biologically active amin** or *vasoactive amin** provided no additional articles. Additionally, articles were selected from references in relevant literature.

The following criteria were used to select studies for detailed review from those identified as relevant to the topic: oral challenge study in susceptible persons (ie, persons with a history of adverse reactions to dietary biogenic amines), original data report (no abstract), and publication in a peer-reviewed journal. Dietary elimination studies were not considered because of the great difficulties with blinding and large placebo effects, which make them less useful in assessing causal relations. Toxic food reactions, which can occur in any individual if the dose is high enough, were also not selected for detailed review.

Studies Selected for Detailed Review

Studies with positive results were examined for possible sources of bias that could render the conclusion false positive, whereas studies with negative results were examined for possible sources of noise that could render the conclusion false negative.

Evaluation of Studies With Positive Results

Studies with positive results (ie, studies in which an effect was reported) without a randomized, double-blind, placebo-controlled (randomized DBPC) design were considered ineligible and were not further evaluated. Eligible studies were further evaluated by careful consideration of adequate blinding and randomization, specification of symptoms, description of positive response, the dose given and dose-response relationships, use of medications before and during the study, number of positive responses after test substance and placebo, and adequate statistical testing. Studies of individual patients were only considered if an n = 1 design with repeated randomized DBPC challenges was used.[4]

Evaluation of Studies With Negative Results

Studies with negative results (ie, studies in which no effect was reported) were eligible whether open or double-blind challenges were used, since open challenges are not prone to false-negative test results. All studies with negative results were examined for factors in their design or methods that could account for the absence of a reported effect (eg, inappropriate selection of patients, small sample size, high number of placebo reactions, high [potentially suppressive] medication levels, short duration of observation period, and soft outcome parameters).[5] Results of methodologically weak or flawed studies (with positive or negative results) were considered inconclusive.

RESULTS

Histamine in Wine

For histamine, 4 oral challenge studies in susceptible patients were found, 2 of which had positive results.[6,7] All 4 challenge studies were designed to test the hypothesis that the level of histamine (and other amines) in red wine is responsible for adverse reactions after wine consumption. Both positive result studies were considered ineligible either because no DBPC design was used[6] or because the challenge was not repeated in the n = 1 design.[7]

The studies with negative results were both considered eligible. Table 1 shows the design and results of these studies. Kanny et al[8] administered 190 mL of a histamine-poor wine (0.4 mg/L) and a histamine-rich wine (13.8 mg/L) to 16 patients with a history of chronic urticaria and wine intolerance. Aside from urticaria, the symptoms reported were headache, flush, decreased blood pressure, increased heart rate, and gastrointestinal symptoms. No difference was found in the number of patients who responded to the histamine-poor (14 patients) or the histamine-rich (15 patients) wine. However, the high percentage (87%) of responses to the placebo could be responsible for the absence of an effect in this study. Therefore, the results of this study cannot be considered conclusive.

Conclusive evidence was provided by Dahl et al,[9] who tested 3 wines with different amine and sulfite contents in 18 patients with a history of red wine–provoked asthma. The wine with the higher sulfite content elicited significantly more frequent bronchoconstrictive responses compared with the other 2 wines. However, no significant difference was found between the response to the original wine and the wine with the lower amine content. Although the exact type and amount of amines were not indicated in this study, it shows that there is no relation between the amine content of red wine and adverse reactions. Thus, one conclusive negative result study was found on the relation between biogenic amines in red wine and wine intolerance. No conclusive positive result studies were found.

Tyramine and Migraine

For tyramine, 12 studies were found, 6 of which had E. Hanington either as the senior or a secondary author.[2,10–14] As observed by Kohlenberg,[15] it appears that the procedure for giving oral tyramine was the same in all of the Hanington studies and that there was considerable overlap in use of data from study to study. The data thus appear to be cumulative, and each study should not be viewed as involving a separate group. Therefore, we will treat the Hanington studies as one single study with 45 patients. Six other studies on the relation between dietary tyramine and intolerance were considered. All were designed to evaluate the ability of oral tyramine to

Table 1. Eligible Challenge Studies Concerning the Relation between the Level of Histamine and Other Amines in Red Wine and Adverse Reactions

Source, y	Substance and dose	Population	Design	Outcome variable(s)	Symptoms	Results	Remarks
Dahl et al,[9] 1986	Histamine in red wine, samples of 10, 25, 50, 100, and 200 mL; 3 different wines were used: low sulphite and high amine (9 mg/L), high sulphite and high amine, and low sulphite and low amine	8 Women, and 10 men; mean age, 41 y and 46 y, respectively; all with history of red wine–provoked asthma	Randomized DBPC oral challenge; 3 different wines were consumed 1 week apart; samples were given at 15-min intervals, if no response was observed, the next sample was administered; PEF was measured at t = 0, t = 5, t = 10 and t = 15 min after each sample; FEV_1 was measured at t = 0 and t = 15 min after each sample	Decrease in PEFR of >15% compared to t = 0 considered as positive response	Tightness of the chest, asthmatic attack, shortness of breath, wheezing	9/19 Subjects had 1 or more positive reactions; wine with high sulphite content elicited a higher bronchoconstrictive response compared with the other 2 wines ($P < 0.01$); no significant difference between response to original wine and wine with lower amine content; sulphite must be the major cause of red wine–provoked asthma	Negative result study conclusive, no relation between (hist)amine content of red wine and tolerance to wine in patients with history of red wine–provoked asthma
Kanny et al,[8] 2001	Histamine in 190 mL of red wine; wine A, 0.4 mg/L; wine B, 13.8 mg/L; sulphites in wine A, 90 mg/L; in wine B, 65 mg/L; tyramine and putrescine higher in wine B; PEA and cadaverine equal in wine A and B	11 Women and 5 men; mean age, 43 ± 13 y; all with chronic urticaria and wine intolerance; no asthma or intolerance to sulphites	DBPC oral challenge; blood was taken at t = 0, 10, 30, and 45 min; urine was collected 5 h before and 5 h after t = 0	Onset of symptoms, plasma (methyl) histamine, urine methyl-histamine, and MIAA	Increased heart rate, decreased blood pressure, flush, urticaria, headache, gastrointestinal symptoms	No difference in number of patients with symptoms after wine A (15 patients) and wine B (14 patients); at t = 10 plasma histamine was significantly higher after wine A than after wine B ($P < 0.05$); plasma and urine methylhistamine and MIAA remained stable	Negative result study inconclusive; reasons: high percentage of responses to the placebo (87%)

Abbreviations: DBPC, double-blind, placebo-controlled; FEV_1, forced expiratory volume in 1 second; MIAA, methylimidazolacetic acid; PEA, phenylethylamine; PEFR, peak expiratory flow rate; t, point in time.

Table 2. Eligible Challenge Studies Concerning the Relation between Oral Tyramine and Migraine

Source, y	Substance and dose	Population	Design	Outcome variable(s)	Symptoms	Results and conclusion	Remarks
Hanington studies,[2,10–14] 1967–1979	125 mg of tyramine in capsule; placebo: 100 mg of lactose in capsule	Patients: 45 migraine patients sensitive to foods high in tyramine; controls: nondietary migraine patients or nonmigrainous control subjects	DBPC oral challenge; tyramine and placebo capsules were sent by mail to each patient with instruction on how they should be taken; completed questionnaire should be returned 24 h after taking the capsule	Headache development	Headache	Overall headache rate in dietary migraine patients, 80% after tyramine vs 8% after placebo; overall headache rate in controls, 0%–15%; tyramine has an effect in inducing migrainous headache in sensitive subjects	Positive result study inconclusive; reasons: more tyramine capsules than placebo capsules, no randomization (tyramine first)
Forsythe and Redmond,[17] 1974 Study 1	100 mg of tyramine in capsule; placebo: 100 mg of lactose in capsule	59 Children with migraine aged 4–14 y; 36 boys and 23 girls	DBPC oral challenge; 1 tyramine capsule and 1 placebo capsule were sent to parents by mail; second capsule should be taken 48 h after first capsule	Headache development	Headache	12 Children developed headache after tyramine, 10 after placebo and 4 after both; trial should be repeated because of shortcomings	Negative result study inconclusive; reasons: inappropriate selection of patients, parents were told about content capsules
Study 2	100 mg of tyramine in capsule; placebo: 100 mg of lactose in capsule	38 Children with migraine aged 4–14 y; 22 boys and 16 girls (these children were not included in the first trial)	DBPC oral challenge; 1 tyramine capsule and 1 placebo capsule were sent to parents by mail; second capsule was posted 1 week after first record sheet was returned	Headache development	Headache	5 Children developed headache after tyramine, 11 after placebo and 4 after both; a positive tyramine test result is of doubtful value in children	Negative result study inconclusive; reasons: inappropriate selection of patients
Ziegler and Stewart,[18] 1977	200 mg of tyramine in capsule; placebo: lactose in capsule	80 migraine patients aged 21–55 y	Randomized DBPC oral challenge	Headache development	Headache	20/80 Patients developed headache after tyramine vs 23/80 after placebo; 12 of these patients developed headache after both tyramine and placebo; production of headache by tyramine is a rare phenomenon and not reproducible	Negative result study inconclusive; reasons: inappropriate selection of patients
Littlewood et al,[16] 1988	Tyramine in 300 mL of red wine, 2 mg/L; placebo: 300 ml of vodka and lemon mixture (equivalent alcohol content)	Patients: 19 patients with suspected red wine–provoked migraine; 5 patients with nondietary migraine; controls: 8 healthy subjects; none of the patients and controls were using medication	DBPC oral challenge; red wine–sensitive patients received red wine (n = 11) or placebo (n = 8); nondietary migraine patients and controls only received red wine	Headache development	Headache	9/11 Red wine–sensitive patients developed headache after red wine vs 0/8 after placebo ($P < 0.001$); none of nondietary migraine patients and controls developed headache after red wine; tyramine content is too low to have any pharmacological action; there must be another substance in red wine (neither tyramine nor alcohol) that provokes headaches in susceptible patients	Positive result study inconclusive; reasons: blinding questionable and not validated

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Table 2. *Continued from page 236*

Source, y	Substance and dose	Population	Design	Outcome variable(s)	Symptoms	Results and conclusion	Remarks
Moffett et al,[19] 1972	125 mg of tyramine in capsule placebo: 125 mg of lactose in capsule	25 Women with migraine aged 20–57 y, 10 with migraine alone (group A), 7 with migraine and epilepsy (group B), 8 tyramine sensitive (group C)	DBPC oral challenge; occurrence of headache was assessed by interview, EEG was recorded, and blood pressure was measured; medication use was continued	Headache development, EEG Abnormalities, blood pressure	Headache	Group A: 1 patient developed headache after placebo; group B: 1 patient developed headache after tyramine, group C: 2 patients developed headache after tyramine, 2 after placebo, and 3 after both; no change in blood pressure after tyramine ingestion; more abnormalities in EEG after tyramine ingestion than after the placebo ingestion	Negative result study conclusive; 125 mg of oral tyramine did not precipitate more headaches than placebo in female migraine patients
Ryan,[20] 1974	125 mg of tyramine in capsule; placebo: unspecified	65 Migraine patients 27 with a positive dietary history (group 1), 13 with a positive alcohol history (group 2), and 35 with a negative dietary history (group 3)	DBPC oral challenge; a second challenge was done with 250 mg of tyramine	Headache development	Headache	Group 1: 10 patients developed headache after tyramine; 5 after placebo, and 9 after both; group 2: 1 patient developed headache after tyramine, 6 after placebo, and 1 after both; group 3: 3 patients developed headache after tyramine, 5 after placebo, and 7 after both; in second challenge no significant difference between number of headaches after tyramine and placebo	Negative result study conclusive; 125 mg of oral tyramine did not precipitate more headaches than placebo in dietary or nondietary migraine patients

Abbreviations: DBPC, double-blind, placebo-controlled; EEG, electroencephalogram.

induce migraine attacks in migraine patients. The Hanington studies and the study by Littlewood et al[16] had positive results, whereas the other 5 studies had negative results. All studies were considered eligible. The design and results of each study are shown in Table 2.

Edda Hanington was a pioneer in the area of oral tyramine and migraine.[2] To examine the effect of oral tyramine in migraine patients, she conducted several challenge studies. Generally, 4 to 5 capsules were sent to each patient by post, and a questionnaire was to be completed and returned 24 hours after taking the capsule. Patients selected for the Hanington studies were only classified as dietary migraine patients when they excluded from their diet those foods that they thought precipitated their attacks. The studies showed spectacular results: an overall headache rate of 80% after ingestion of tyramine capsules (125 mg) compared with 8% after placebo (100 mg of lactose). Whenever nondietary migraine patients or nonmigrainous control subjects were challenged, a low headache rate (0% to 15%) was observed. However, requirements for scientific research have changed since then (1967–1979). A major concern is that Hanington's reports give the impression that ingestion of the tyramine capsules preceded ingestion of the placebo capsule, so time or period effects cannot be ruled out. Furthermore, patients received more tyramine capsules than placebo capsules, thus enhancing the chances of tyramine ingestion preceding headache. Because of these drawbacks, the Hanington studies are considered inconclusive.

Forsythe and Redmond[17] undertook a double-blind controlled trial with children with migraine. In contrast to the Hanington studies, no attempt was made to select patients who reported dietary associations with migraine occurrence. In the first trial, 59 children were challenged with a tyramine capsule (100 g) and a lactose capsule (100 g). Sixteen children developed a headache after the tyramine capsule vs 14 children after the placebo. However, this negative result study cannot be considered conclusive because the parents of the children were told about the contents of the capsules and because the selection of patients was inappropriate.

A second trial was initiated to remove some shortcomings of the first one. In this trial, the parents were not told about the contents of the capsules. Thirty-eight children with migraine, not included in the first trial, were selected for this study. Again, sensitivity to tyramine-containing foods was not a criterion for selection. Nine of the children developed a headache after the tyramine capsule vs 15 children after the placebo. However, the problem of inappropriate selection of patients also makes the results of this second trial inconclusive.

In 1977, Ziegler and Stewart[18] challenged 80 migraine patients with a tyramine capsule (200 mg) and a placebo capsule (lactose). No difference was found in the number of patients who developed a headache following the ingestion of the tyramine capsule (20 patients) compared with the placebo (23 patients). However, the selection of patients in this study is inappropriate, since sensitivity to tyramine-containing foods was not considered. Therefore, the negative results of this study are inconclusive.

Littlewood et al[16] performed a study with 300 mL of red wine and 300 mL of a vodka and lemon mixture as placebo. All drinks were chilled to obscure the flavor and served in a brown glass bottle with a dark straw to conceal the color. Twenty-four migraine patients, of whom 19 were sensitive to red wine, participated in the experiment, as well as 8 healthy controls. Eleven of the 19 red wine–sensitive patients received red wine and 8 of them received placebo. The 5 migraine patients who were not sensitive to red wine and the 8 controls received red wine. In this randomized DBPC study, a clear effect of red wine could be seen: 9 of 11 red wine–sensitive migraine patients developed a headache after red wine vs 0 of 8 red wine–sensitive migraine patients after vodka. None of the other migraine patients or controls developed a headache after the red wine. However, the blinding of this study is uncertain, since the taste difference between red wine and vodka is difficult to obscure and challenge materials were not validated in this respect. Therefore, the study of Littlewood et al is considered inconclusive.

Conclusive evidence was provided by Moffett et al,[19] who challenged 25 women with migraine with a tyramine (125 mg) and a placebo capsule (125 mg of lactose). The group consisted of 10 patients with migraine alone (group A), 7 patients with migraine and epilepsy (group B), and 8 patients who had noticed that certain foods that contained tyramine could precipitate their migraine attacks (group C). The capsules were ingested at home on the morning of attendance to the department. Of 50 challenges, 12 headaches occurred. One headache followed placebo in group A and one followed tyramine in group B. In group C, 2 headaches occurred after tyramine, 2 after placebo, and 6 after both test capsules. Thus, this study shows no relation between the ingestion of tyramine and headache attacks in migraine patients.

The negative result study by Ryan[20] further supports these results. In this study, 65 migraine patients were challenged with either 125 mg of tyramine in a capsule or a placebo. In the first group, which consisted of 27 patients with a positive dietary history (ie, patients reporting dietary associations with migraine occurrence), 19 patients developed headache after tyramine vs 14 after placebo. In group 2 (13 patients with a history of alcohol use), 2 patients developed headache after tyramine vs 7 after placebo. In the third group, which consisted of 35 patients with a negative dietary history, 10 patients developed headache after tyramine vs 12 after placebo. Thus, in this conclusive study the oral ingestion of tyramine did not precipitate migraine in dietary or nondietary migraine patients.

Thus, 2 conclusive negative studies were found on the relation between oral tyramine and headache attacks in migraine patients. No conclusive positive result studies were found.

Phenylethylamine and Headache

Two oral challenge studies with phenylethylamine were found. Both studies were designed to evaluate the ability of oral phenylethylamine to induce headache attacks in patients

Table 3. Eligible Challenge Studies Concerning the Relation between Oral PEA and Headache

Source, y	Substance and dose	Population	Design	Outcome variable(s)	Symptoms	Results	Remarks
Marcus et al,[22] 1997	PEA in 60 g of chocolate, 1.9 μg/g; placebo: PEA in 60 g of carob, 0.4 μg/g; blinding was validated (nonsignificant κ)	63 Women; mean age, 28 y; all with chronic headache; 11 of them reporting that chocolate was a trigger for their headaches	Randomized DBPC oral challenge; restricted diet (tyramine, histamine, PEA, nitrites, caffeine, MSG, aspartame) 2 weeks before test	Headache development	Headache	11/63 patients (of whom 2 were chocolate sensitive) developed headache after chocolate vs 26/63 patients (of whom 4 were chocolate sensitive) after placebo	Negative result study conclusive; chocolate does not induce more headaches than carob in a general sample of female headache patients

Abbreviations: DBPC, double-blind, placebo-controlled; MSG, monosodium glutamate; PEA, phenylethylamine.

with headache. One study reported positive results and one reported negative results. The positive study was considered ineligible, because the challenges were not randomized.[21]

The design and results of the eligible study are shown in Table 3. In this study, performed by Marcus et al,[22] 63 women with chronic headaches (11 of them reporting that chocolate was a trigger for their headaches) were challenged with 60 g of chocolate (1.6 μg/g of phenylethylamine) and 60 g of carob (0.4 μg/g of phenylethylamine). The chocolate and carob products were supplemented with mint flavoring to mask natural differences in taste. The number of patients reporting headaches after the challenge did not differ between the chocolate group (11 patients, of which 2 were chocolate sensitive) and the carob group (26 subjects, of which 4 were chocolate sensitive). This conclusive negative result study does not demonstrate a relation between oral phenylethylamine and headache.

Thus, 1 conclusive negative result study was found on the relation between oral phenylethylamine and headache attacks in headache patients. No conclusive positive result studies were found.

DISCUSSION

In this review, no evidence was found for the hypothesis that histamine, tyramine, or phenylethylamine can cause food intolerance reactions in susceptible subjects. Four conclusive studies provided negative results, and no conclusive positive studies could be found. Table 4 shows the total number of eligible studies.

Adverse reactions as a result of biogenic amines are often classified as intolerance reactions, also called pseudoallergy or false food allergy. Intolerance is a form of hypersensitivity, which is not mediated by the immune system, in contrast to allergic reactions. The operative mechanism in food intolerance reactions may be enzymatic, but often the biological mechanism is unknown. However, adverse reactions after the oral ingestion of histamine can be indistinguishable from allergic symptoms, since histamine is also a mediator in allergic reactions.

In the human, endogenously synthesized biogenic amines fulfill important metabolic functions in the nervous system and in the control of blood pressure. To prevent dietary biogenic amines from entering the systemic circulation, humans possess a system of metabolizing enzymes, mostly located in the intestines but also in the liver, lung, blood platelets, stomach, spleen, and kidneys. The most important enzymes implicated are monoamine oxidases A and B, diamine oxidase, phenolsulfotransferase M, and histamine *N*-methyltransferase.

There are some indications for a decreased level of intestinal diamine oxidase in patients with chronic urticaria[23–26] and for a decreased level of monoamine oxidase B and phenolsulfotransferase M in blood platelets of migraine patients.[27,28] However, these metabolic findings do not seem to have any clinical consequences, since they are not supported by oral challenge studies in susceptible patients.

Table 4. Eligible Studies Concerning the Relation between Food Intolerance and Dietary Histamine, Tyramine, and Phenylethylamine

	Conclusive studies		Inconclusive studies	
	Positive results	Negative results	Positive results	Negative results
Histamine				
Wine intolerance	0	1	0	1
Tyramine				
Migraine	0	2	2	4
Phenylethylamine				
Headache	0	1	0	0

Biogenic amines might easily interact with each other and with other substances in food. For example, ethanol in red wine might inhibit biogenic amine–metabolizing enzymes. Phenolic flavonoids, such as anthocyanins and catechins, might inhibit phenolsulfotransferase.[29,30] Biogenic amines other than histamine, such as tyramine, phenylethylamine, putrescine, and cadaverine, might competitively and noncompetitively inhibit diamine oxidase and histamine *N*-methyltransferase.[31,32] However, the occurrence of symptoms that result from such interactions remains hypothetical, because there are no acceptable clinical studies that demonstrate such reactions.

CONCLUSION

Of the studies performed on the adverse effects of biogenic amines, only a few are methodologically acceptable. Although this limits the conclusions that may be reached, the current scientific literature does not show a relation between the oral ingestion of biogenic amines and food intolerance reactions. There is therefore no scientific basis for dietary recommendations concerning biogenic amines in such patients.

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CME Examination

1–5, Jansen SC, van Dusseldorp M, Botema KC, Dubois AE. 2003;91:233–241.

Self-Assessment Exam Questions

1. Which of the following statements is *not* correct?
   a. Biogenic amines are present in foods such as soy products, sauerkraut, chocolate, and cheese.
   b. Biogenic amines in foods are always produced by bacteria as part of the production process.
   c. Tyramine, histamine, phenylethylamine, and tryptamine belong to the group of biogenic amines.
   d. Biogenic amines can be synthesized endogenously.
2. The studies on the relation between oral tyramine and migraine, performed by Hanington, cannot be considered conclusive because:
   a. These studies were not placebo-controlled.
   b. Administration of placebo and tyramine was not in randomized order.
   c. The number of patients was too small.
   d. Only women participated in these studies.
3. The state of the art regarding the relation between the ingestion of oral biogenic amines and food intolerance reactions is:
   a. There is no evidence for such a relation, and dietary recommendations concerning biogenic amines should be continued.
   b. Some studies with positive and negative results are available, but so far the results are inconclusive.
   c. The conclusive studies available so far show no relation between the ingestion of biogenic amines and food intolerance reactions.
   d. The studies published so far suggest a relation between ingestion of biogenic amines and food intolerance reactions.
4. Which of the following methodological drawbacks does *not* pertain to the use of dietary elimination studies to assess the role of food as the cause of symptoms in a positive result study:
   a. Dietary studies have a considerable placebo effect.
   b. Dietary studies are difficult to blind.
   c. Compliance is more difficult to assess in dietary studies.
   d. Dietary studies are more difficult to randomize.
5. In a negative result study (where no effect of a food is found), all of the following considerations are important possible causes of false-negative study results, *except*:
   a. Poor blinding
   b. Poor patient selection
   c. Small sample size
   d. High levels of medication use

Answers found on page 296.